Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.

Online Appendix

ADOPT Adjudication Committee Procedures

As part of its mandate, the ADOPT Steering Committee periodically monitored the overall hazard rate of monotherapy failure in the combined cohort, masked to treatment group differences. During a September, 2003 data review, the Steering Committee was concerned by the high incidence of initial fasting plasma glucose values >180 mg/dl that were not subsequently followed by repeat testing due to withdrawal from the study, and the high incidence of withdrawals due to insufficient therapeutic effect. As a result, the protocol was amended to establish an independent adjudication committee to review all such cases and to determine whether each represented a primary outcome.

The Adjudication Committee consisted of three independent physicians, experienced in the management of diabetes and familiar with the conduct of clinical trials. The Adjudication Committee decided to count an event as a primary outcome if:

- it was probable that the event would have met the protocol definition of monotherapy failure if the participant had remained in the study and if all evaluations were performed as specified precisely by the protocol,

  AND

- the event satisfied usual good clinical practice criteria for monotherapy failure.

Cases that were evaluated by the Adjudication Committee to determine if they were likely to have been a monotherapy failure if the protocol definitions had been followed included participants:

- with a final fasting plasma glucose >180 mg/dl (10 mmol/l) without a follow-up fasting plasma glucose,
- with consecutive fasting plasma glucose levels >180 mg/dl (10 mmol/l) which did not meet the timing requirements relative to maximum-tolerated dose or where there was uncertainty about whether maximum-tolerated dose has been achieved ,
- withdrawn due to insufficient therapeutic effect or declared by the investigator to be a monotherapy failure, but who did not meet the protocol definition, or
- who were placed on combination oral agent or insulin therapy as a protocol violation.

The Sponsor supplied to the Adjudication Committee the following blinded data outputs for those participants who concluded the study and did not meet the strict protocol definition of monotherapy failure due to non-compliance with the protocol or early withdrawal:

- Patient identification number
- Demographic information
- Medical history/baseline signs and symptoms
- Prior and concomitant medications
- Adverse event reports
- Serious adverse events reports
- Laboratory information
- Dose level of study medication

- Reason for withdrawal
- Any additional data requested by the committee (however, the Adjudication Committee was not be able to request additional assessments to be performed on the participant).

All information was obtained from the relevant case report forms and the central laboratory reports and formatted by the Biometrics group of the Sponsor.

Each Adjudication Committee member reviewed each case independently and indicated whether the subject should be considered a monotherapy failure (Yes/No). When the decision was unanimous, no further action was required. Otherwise, the committee conferred to discuss the case and a two-thirds majority vote determined the classification of that subject. All Adjudication Committee decisions were recorded on specially designed case report forms and were added to the study database. The Adjudication Committee's results were used in the primary efficacy analysis along with those participants with monotherapy failure based on confirmed fasting plasma glucose tests that satisfied the protocol definition.

Online Appendix

List of Key Efficacy and Safety Results Confirmed by Independent Academic Statisticians

The following key results were confirmed by one of the two external statisticians:

- Proportional hazards regression analysis of time to monotherapy failure
- Kaplan-Meier cumulative incidence of monotherapy failure
- Subgroup analyses of monotherapy failure (age, body mass index, gender)
- Longitudinal model analysis of fasting plasma glucose, HbA1c, HOMA %B, HOMA %S, weight
- Counts of fatalities
- Adverse event counts

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Additional Statistical Methods

The cumulative incidence of time-to-event variables was estimated by the modified Kaplan-Meier method for periodic assessments[1] with deaths right censored, and also using Gray's method[2] with death as a competing risk. Other premature exits were censored at the time of exit. The Wald test of the difference between groups and the estimate of the risk reduction in the cause-specific hazard were obtained from a proportional hazard regression model[3] adjusted for baseline HbA1c and gender, and stratified by country and presence or absence of a baseline HbA1c. A sensitivity analysis assessed the potential bias due to losses to follow-up.[4] Differences in pair-wise treatment effects among subgroups (pre-specified for age, gender, BMI) were tested using a subgroup by treatment interaction in a proportional hazards regression model, with significance of the interactions determined using the Hochberg adjustment. Proportional hazards regression models were used to test for differences between groups in other event-time variables (e.g., cardiovascular disease events).

A normal errors longitudinal model[5] was fit to the post-randomization means of quantitative variables up to the time of monotherapy failure, withdrawal or end of study. The model included treatment, time of measurement and their interaction, adjusted for baseline values, country and gender with an unstructured covariance matrix. The protocol specified that the difference between treatments be tested at 4 years, at which time the maximal number of subjects had the longest duration of follow-up. A slope (rate of change) was calculated from values starting at 6 months of treatment (to disregard the initial acute effects of therapy) and extending to 5 years. Parameters were log-transformed as appropriate. To allow for possible effects of informatively

missing data, a multivariate rank analysis[6] was conducted with an untied worst rank[7] assigned to subjects following monotherapy failure or withdrawal due to insufficient therapeutic effect.

Differences in proportions were tested using the contingency χ^2-test and differences in quantitative or ordinal variables using the Kruskal-Wallis test.

Analyses were conducted using SAS® (SAS Institute, Cary NC).

References:

1. Lachin JM. Biostatistical Methods. The Assessment of Relative Risks. New York: John Wiley & Sons, 2000.
2. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist 1988; 16:1141-1154.
3. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons, 2002.
4. Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials 2000; 21:167-189.
5. McCulloch CE, Searle SR. Generalized, Linear and Mixed Models. New York: John Wiley & Sons, 2001.
6. Lachin JM. Some large sample distribution-free estimators and tests for multivariate partially incomplete data from two populations. Stat in Med 1992; 11:1151-1170.
7. Lachin JM. Worst-rank score analysis with informatively missing observations in clinical trials. Control Clin Trials 1999; 20:408-422.

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Sensitivity Analysis for the Primary Outcome

A sensitivity analysis was performed for the primary outcome using Lachin's method for the assessment of the potential impact of bias introduced by withdrawals and losses-to-follow-up in the test for proportions.[1] For each pair-wise comparison, the bias is determined that would be necessary to negate the statistical significance of the observed difference between groups.

The observed proportions with monotherapy failure among those evaluated with rosiglitazone, metformin and glyburide, respectively, were *Pr =143/917 = 0.156, Pm = 207/903 = 0.229,* and *Pg = 311/807 = 0.385*. Lachin's method was applied to the two primary pair-wise comparisons.

For the comparison of rosiglitazone versus glyburide, the observed difference in proportions of (0.385 – 0.156) = 0.229 was highly significant with $P<0.001$. This significance would be negated if the bias introduced by selective withdrawals was at least 0.181. If it was assumed that there was no bias in the glyburide group, and that all of the bias arose only in the rosiglitazone group, then the true proportion in the rosiglitazone group would have to have been >0.156 + 0.181 = 0.337 for the results to no longer be significant. Thus, the true numbers of monotherapy failures with rosiglitazone had the withdrawals been completely unbiased would have to be more than twice that reported in order to negate the statistically significant benefit with rosiglitazone. We consider this highly unlikely given the other analyses presented elsewhere of the characteristics of withdrawals and their impact on the observed treatment effect. The fact that the subgroup

analyses demonstrated consistent benefit among all subgroups also suggests that these results were not due to differential bias introduced by withdrawals.

For the rosiglitazone versus metformin comparison, the observed difference in proportions was 0.229 – 0.156 = 0.073 and a bias of 0.032 or greater would negate the beneficial effect. This represents an increase of at least 20.5% in the proportion with rosiglitazone. Given the large number of such withdrawals, a bias of this magnitude cannot be ruled out. However, the characteristics of the participants who withdrew did not differ amongst treatment groups and the subgroup analyses demonstrated some benefit in all subgroups. These observations suggest that the beneficial effect of rosiglitazone versus metformin is robust and was unlikely to be due to a bias.

Reference:

1. Lachin JM. Statistical considerations in the intent-to-treat principle. Controlled Clinical Trials 21: 167-189; 2000.

Figure Legends for Online Appendix

Appendix Figure 1: Kaplan-Meier estimate of the cumulative incidence of confirmed fasting plasma glucose >140 mg/dl (>7.8 mmol/l) for participants randomized with fasting plasma glucose ≤140 mg/dl. Risk reduction is listed for pair-wise group comparisons from a baseline covariate-adjusted Cox proportional hazards model.

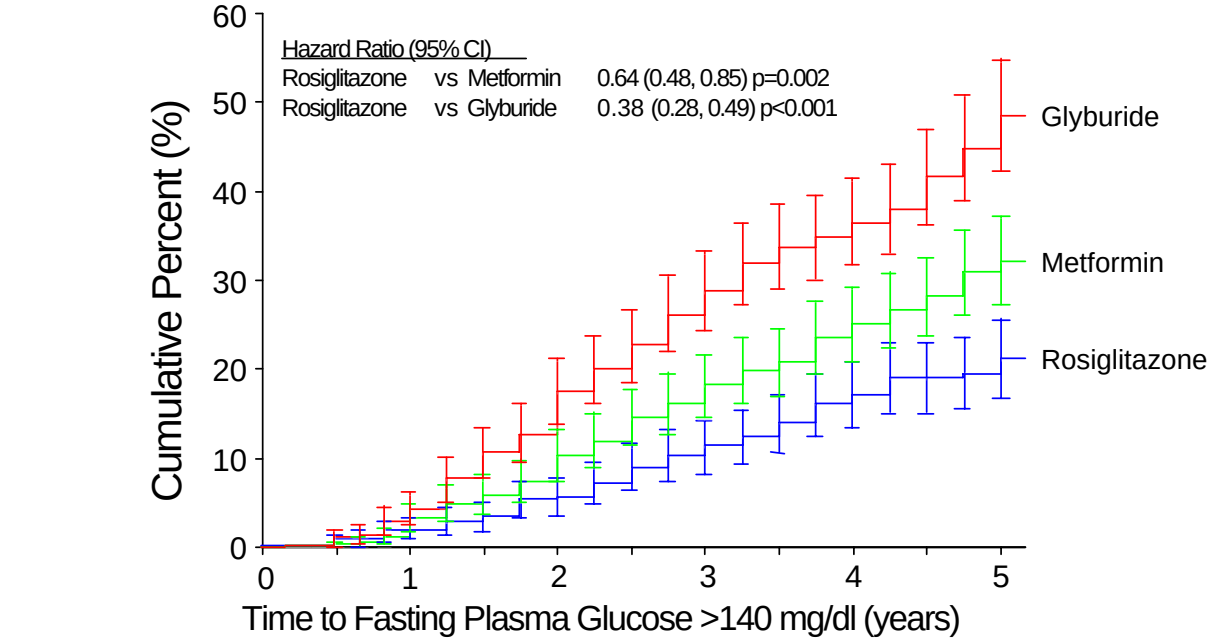
Appendix Figure 2: Multivariate rank analysis[1] with an untied worst rank assigned to subjects following monotherapy failure or withdrawal due to insufficient therapeutic effect for A) fasting plasma glucose, and B) HbA1c by treatment group over time. For all figures, data are presented as median with treatment differences at 4 years.

Reference:

1. Lachin JM. Some large sample distribution-free estimators and tests for multivariate partially incomplete data from two populations. Stat in Med 1992; 11:1151-1170.

Online Appendix

Figure 1



Participants at Risk						
Rosiglitazone	511	445	393	351	295	107
Metformin	520	456	402	348	296	112
Glyburide	480	412	343	264	200	63

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Figure 2A

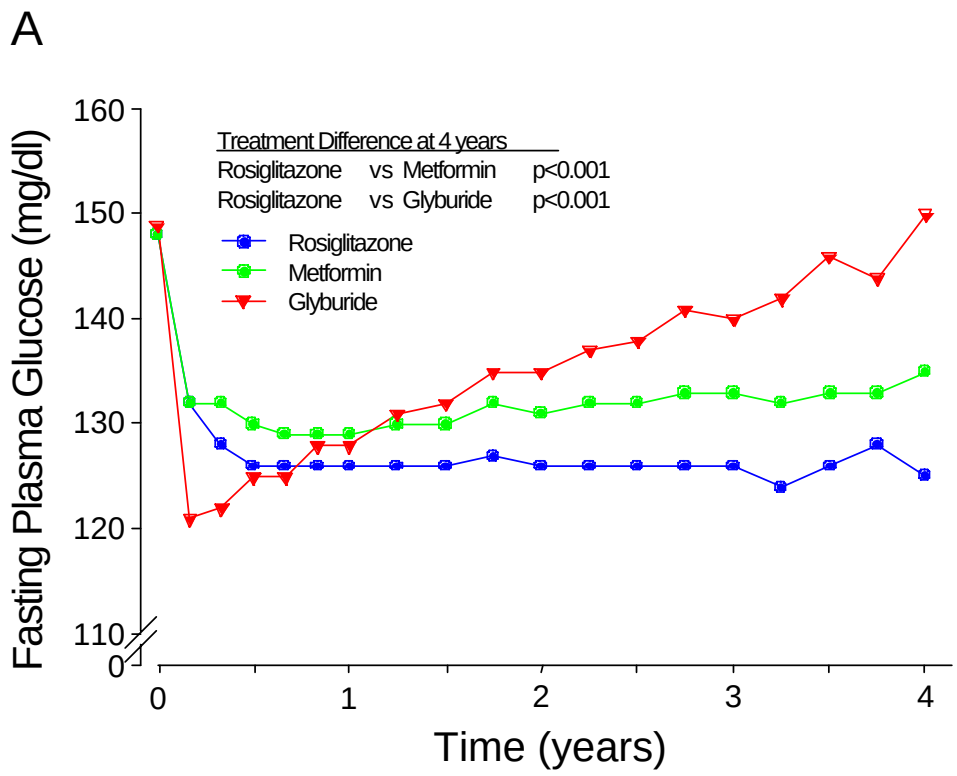

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Figure 2B